REMARKS/ARGUMENTS

Claims 48-59 are pending following entry of the above amendments to the claims.

New claims 48-59 find support in cancelled claims 27-32 and 47 and on page 3, lines 7-9 and on page 3, line 22 to page 4, line 19 of the specification.

Applicants also submit herewith an Information Disclosure Statement and accompanying 1449 form listing US patents 6,268,343 and 6,458,924 and note that an application in the same patent family, USSN 10/285,079, is currently pending before the USPTO.

Applicants also note that they have never received an Examiner-initialed copy of the 1449 form filed on January 30, 2001 (courtesy copy attached) and accordingly, respectfully request that the Examiner initial the aforementioned 1449 form and attach it to the next communication mailed to Applicants.

REJECTION OF THE CLAIMS UNDER 35 U.S.C. 112, FIRST PARAGRAPH

The Examiner rejected claims 20-32 and 34-46 under 112, first paragraph because the specification "while being enabling for SEQ ID NO:2 or a specific GLP-1 analog having the same amino acid sequence as SEQ ID NO: 2 with a lipophilic substituent attached to the C-terminal amino acid...., does not reasonably provide enablement for a derivative of GLP-1 or an analog or a fragment, or a derivative of GLP-2 or an analog or a fragment, wherein the lipophilic substituent optionally via a spacer is attached to the N-terminal or C-terminal amino acid of GLP-1 or GLP-2 where the sequences of GLP-1 or GLP-2 analogs or fragments are not defined" (page 3 of Office Action).

In particular, the Examiner alleges that the specification "only discloses cursory conclusions without data supporting the findings, which state that the invention relates to the derivatives of peptide hormones such as GLP-1 or GLP-2 which have been modified by introducing lipophilic substituent comprising 8-40 carbon atoms in either the N-terminal or C-terminal amino acid of the native peptide or analog thereof" (page 3 of the Office

Action). The Examiner then concludes that "[T] present application provides no indicia and no teaching/guidance as to how the full scope of the claims is enabled" (page 4 of the Office Action) and repeatedly cites to the fact that the only working example presented is that of a single GLP-1 sequence SEQ ID NO: 2.

With all due respect, Applicants disagree.

Here, the pending claims as amended are now directed to C-terminally modified GLP-1 or analogs thereof where the modification is the attachment of an 8-40 carbon lipophilic group optionally via a spacer, to the C-terminal amino acid of the aforementioned GLP-1 or analogs thereof. The application teaches that the claimed derivatives are produced via the formation of an amide bond between the lipophilic group (or the spacer) and the C-terminally modified amino acid (see, for example, pages 3-4 of the application). The application further teaches that the derivatives of the invention have a protracted profile of action relative to the unmodified parent peptide and that one measurement of protraction can be obtained by measuring the disappearance rate of the derivatives in pigs following subcutaneous injection (see page 2, lines 17-18 and page 12, line 36 to page 13, line 26 of the application)

As stated by the court in In re Marzocchi, "it is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. Otherwise, there would be no need for the applicant to go to the trouble and expense of supporting his presumptively accurate disclosure." 169 USPQ 367, 370 (CCPA 1971).

Here, it is Applicants' position that the Examiner has failed to satisfy the initial burden on the Patent Office to prove a prima facie case of nonenablement.

As noted above, the Examiner's rejection is based on the presence of only a single example for GLP-1 derivatives in the application and the assertion that the specification on pages 2-5 "only discloses cursory conclusions without data supporting the findings". In addition, the statement by the Examiner that "the sequences of GLP-1 or GLP-2 analogs or

fragments are not defined" (page 3 of the Office Action) suggests that the Examiner considers this to be missing information that is critical to the enablement of the claimed invention.

However, in response, Applicants note that it is well settled that compliance with the enablement requirement of section 112, first paragraph, does not turn on whether a working example is disclosed (see MPEP 2164.02). Thus, the presence of only a single working example of the claimed GLP-1 derivatives does not mean that claims to such products are nonenabled.

Moreover, the Examiner fails to describe why the teachings on pages 2-5 of the application would not enable one to successfully produce the claimed derivatives via the formation an amide bond between the lipophilic group (or the spacer) and the C-terminal amino acid of the peptide. Indeed, Applicants submit that the chemistry underlying the formation of amide bonds was well understood at the time of filing of the present application and the fact that amide bonds can readily be formed between lipophilic groups and different peptides is provided by the examples in the specification.

Further, as additional evidence that the claimed C-terminally modified GLP-1 derivatives could be readily produced and tested for protraction by following the teachings of the present application, Applicants direct the Examiner's attention to the attached paper by Knudsen et al [J.Med Chem. (2000) 43:1664-1669] and to compounds 8, 27 and 35 (see Table 1) each of which are disclosed to exhibit a protracted plasma half-life relative to GLP-1 (7-37) following subcutaneous administration to pigs (ie the methodology disclosed on page 12, line 36 to page 13, line 26 of the present application).

Finally, with respect to the Examiner's statement that "the sequences of GLP-1 or GLP-2 analogs or fragments are not defined", it is Applicants' position that the Examiner fails to state **why** the missing sequence information for the GLP-1 peptides could not be developed or obtained without undue experimentation. In this regard, Applicants note that the sequence of GLP-1 (7-37) was known well before the 1995 priority filing date (see, for example, column 4, lines 5-9 of US patent 5,120,712) of the present application and that methods for preparing analogs of GLP-1 (7-37) were also well known to those of ordinary skill in the art (see, for example, US patent 5, 545,618).

Accordingly, in view of the above arguments and data presented herein, Applicants submit that pending claims 48-59 are fully enabled by the present application.

REJECTION OF THE CLAIMS UNDER 35 U.S.C. 112, SECOND PARAGRAPH

The Examiner rejected claims 20-32 and 34-47 as indefinite because 1) in the terms "GLP-1 or analog or fragment thereof" or "GLP-2 or analog or fragment thereof", it is unclear what amino acid sequence the analog or fragment has and whether the analog or fragment is functional or not (claims 20-32 and 34-47); 2) in the term "Glu-Lys wherein the Lys is attached to the C-terminal amino acid or Asp-Lys wherein the Lys is attached to the C-terminal amino acid" in claims 27 and 41, it is unclear whether the Lys is attached to the C-terminal amino acid of the GLP-1 or Asp-Lys (claims 27-32 and 41-47); 3) it is not clear how Glu or Asp is attached to both the C-terminal amino acid and the lipophilic substituent where the lipophilic substituent is an acyl group but does not have an amino group; and 4) SEQ ID NO 2 in claim 47 does not conform to claim 27.

Applicants respectfully traverse these rejections and address each in turn.

1) all that is required under the second paragraph of section 112 is that a claim term have a clear and definite meaning to one of skill in the art. Here, the claims are directed to C-terminally modified GLP-1 or analogs thereof and the phrase "analogs" is clearly defined at page 2, lines 10-15 of the present application. As to any "function" associated with the analog, the present specification simply discloses that a derivative of such an analog modified at its C-terminal amino acid with a lipophilic group must have a protracted profile of action as measured, for example, by half-life in vivo in pigs. Accordingly, Applicants submit that the phrase "GLP-1 or analogs thereof" has a clear and definite meaning to one of skill in the art.

2 and 3) Applicants respectfully submit that these rejections have been addressed by new claim 48 presented herein; specifically, by the insertion of the phrase "optionally having an amino group" after the lipophilic substituent and by the insertion of a comma between "Glu-Lys wherein the Lys is attached to the C-terminal amino acid" and "or Asp-Lys wherein the Lys is attached to the C-terminal amino acid" as requested by the Examiner.

4) Applicants believe SEQ ID NO: 2 in new claim 56 does conform to independent claim 48 since claim 48 is directed to inter alia "A derivative of GLP-1 or an analog thereof wherein a lipophilic substituent having 8 to 40 carbon atoms and optionally having an amino group is optionally via a spacer attached to the C-terminal amino acid of GLP-1 or the analog thereof and wherein the spacer is Lys, Glu ..." and dependent claim 56 is directed to a derivative of a GLP-1 analog [ie GLP-1 (7-34)] having a C14 group (ie a lipophilic group having an amino group) attached to a C-terminal amino acid (ie the Lys at position 34 of the GLP-1 analog) via a spacer (ie the Glu residue).

Accordingly, in view of the above amendments and remarks, Applicants respectfully request withdrawal of the section 112, second paragraph rejections.

The Examiner is hereby invited to contact the undersigned by telephone if there are any questions concerning this amendment or application.

Please charge any deficiencies or overpayment to Deposit Account No. 14-1447.

Respectfully submitted,

Date: January 2, 2004

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